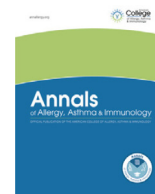




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Letters

Delayed angioedema after administration of the severe acute respiratory syndrome coronavirus 2 messenger RNA vaccine

The coronavirus disease 2019 (COVID-19) pandemic has led to millions of deaths worldwide and continues to be a public health threat. Administration of COVID-19 vaccines safely and markedly decreases the chance of contracting severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and prevents severe COVID-19. Their widespread use is imperative to ending the pandemic. Since their implementation, various adverse reactions to the messenger RNA (mRNA) COVID-19 vaccines have been reported, with the most common being delayed cutaneous reactions, and, rarely, anaphylaxis.^{1–3} Here, we present 3 cases of delayed angioedema after mRNA COVID-19 vaccination (Table 1).

Case 1

A 21-year-old man with a history of chronic rhinitis tolerated his first Pfizer-BioNTech COVID-19 mRNA vaccine without adverse symptoms. Two-and-a-half days after his second dosage (given 3 weeks later), he developed erythematous plaques and wheals on his thigh with subjective tongue swelling. The rash was evanescent but persisted despite antihistamine treatment, becoming more diffuse for more than 30 hours. Five days after his second dosage, he developed marked swelling of his lips with dysphagia, prompting evaluation in the emergency department (ED), where he was found to be normotensive and tachycardic. On physical examination, he was noted to have an urticarial rash on his neck and face, and swelling of the posterior pharynx, tongue, upper lip, and periorbital area. In the ED, he was given 0.3-mg intramuscular epinephrine, 125-mg intravenous methylprednisolone, 20-mg intravenous famotidine, 50-mg intravenous diphenhydramine, and 10-mg oral cetirizine. The patient's angioedema began to improve within 8 hours and completely resolved within 24 hours. He denied previous episodes of angioedema and reported no further episodes in the subsequent 7 months.

Case 2

A 33-year-old man with a history of type 1 diabetes mellitus, allergic rhinitis, peanut allergy, and eosinophilic esophagitis tolerated his first Pfizer-BioNTech COVID-19 mRNA vaccine without immediate adverse symptoms. After 30 hours, he developed throat tightness, dysphagia, and dyspnea. He self-administered 0.3-mg intramuscular epinephrine and presented to the ED, where he was noted to be hypertensive and tachycardic. Physical examination revealed dysphonia, dyspnea, and tripodding. Flexible laryngoscopy revealed

grape-sized uvular swelling and edema of the false vocal folds. He received another dosage of 0.3-mg intramuscular epinephrine, 50-mg intravenous diphenhydramine, and 125-mg intravenous methylprednisolone. Because of the severity of his symptoms, he was started on a continuous intravenous epinephrine infusion that was weaned overnight as the angioedema improved. Serum tryptase level drawn in the ED was normal. The patient denied ingestion of peanuts before symptom onset and had no previous history of angioedema. He received his second Pfizer-BioNTech vaccine 6 months after this reaction without complications. He reported no further episodes of angioedema in the subsequent 9 months after his first vaccination.

Case 3

A 33-year-old woman with a history of episodic idiopathic urticaria, asthma, venom hypersensitivity, and Cushing syndrome on long-term low-dose corticosteroids tolerated her first Pfizer-BioNTech COVID-19 mRNA vaccine without immediate complications. After 1 day, she developed a pruritic, erythematous rash on her chest, throat tightness, and dyspnea, and presented to the ED where she was noted to be normotensive, tachycardic, and mildly febrile. Physical examination revealed lip and tongue angioedema, urticaria involving arms and chest, muffled voice, and decreased breath sounds. Flexible laryngoscopy revealed edematous vocal cords. She was urgently intubated. Serum tryptase levels during symptoms were normal. She received 2 doses of 0.3-mg intramuscular epinephrine, 50-mg oral diphenhydramine, 125-mg intravenous methylprednisolone, and 20-mg oral famotidine. Owing to her symptom severity, she was started on a continuous intravenous epinephrine infusion, which was weaned after 8 hours, and her angioedema resolved by 14 hours. She was advised not to receive dose 2 of the Pfizer-BioNTech COVID-19 vaccine. She denied a previous history of angioedema and reported no further episodes in the subsequent 7 months.

Anaphylaxis to mRNA COVID-19 vaccines is estimated to occur in 2.5 to 11.1 cases per million doses.^{1,4,5} In these cases, diffuse erythematous rash, generalized urticaria, angioedema, wheezing, dyspnea, hypotension, nausea, and vomiting were typically observed within 15 to 30 minutes of administration.^{2,4–6} In contrast, the mean time to symptom development in our 3 cases was 39 hours and, when available, serum tryptase levels collected at the time of symptoms were within the reference range. Urticaria has been reported to develop within 1 to 3 days after vaccination but, in these reports, there was no association with angioedema.^{3,7} Delayed local cutaneous reactions with erythema, induration, and tenderness, which

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Table 1
Overview of Cases of Delayed Angioedema After SARS-CoV-2 mRNA Vaccine Administration

Demographic	Patient 1	Patient 2	Patient 3
Age (y)	21	33	33
Sex	Male	Male	Female
Ethnicity	African American	White	Latino
Atopic history	Chronic rhinitis, no previous history of angioedema	Allergic rhinitis, eosinophilic esophagitis, peanut allergy, asthma, no previous history of angioedema	Allergic rhinitis, intermittent asthma, venom hypersensitivity, chronic spontaneous urticaria, no previous history of angioedema
Miralax exposure	Never taken	Never taken	Unclear if ever taken
Vaccine administered	second dosage Pfizer-BioNTech COVID-19	first dosage Pfizer-BioNTech COVID-19	first dosage Pfizer-BioNTech COVID-19
Onset of symptoms	60 h postvaccination	30 h postvaccination	26 h postvaccination
Symptoms	Urticarial rash, tongue swelling, lip swelling, dysphagia, periorbital swelling	Uvular swelling, dysphagia, dysphonia, and dyspnea	Urticaria, lip swelling, tongue swelling, vocal cord swelling, dysphonia, dysphagia, and dyspnea
Vitals on presentation to the emergency department	BP, 110/68; HR, 100; RR, 18; T, 98.3°F; oxygen saturation 96% on RA	BP, 174/110; HR, 120; RR, 20; T, 98.4°F; oxygen saturation 98% on RA	BP, 95/55; HR, 128; RR, 18; T, 100.6°F; oxygen saturation 98% on RA
Treatment	IM epinephrine, corticosteroid, antihistamine	IM epinephrine, IV epinephrine, corticosteroid, antihistamine	IM epinephrine, IV epinephrine, corticosteroid, antihistamine
Serum tryptase (mcg/L)	Not collected	4.3, normal	2.2, normal
C4 Level (mg/dL)	Not collected	31.5, normal	21.8, normal
Recurrence of angioedema to date	None	None	None

Abbreviations: BP, blood pressure; COVID-19, coronavirus disease 2019; HR, heart rate; IM, intramuscular; IV, intravenous; mRNA, messenger RNA; RA, room air; RR, respiratory rate; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; T, temperature.

developed approximately 8 days and 2 days after first and second vaccinations, respectively, have also been described.^{3,7} However, our cases did not have involvement of the injection site.

Altogether, these cases were disparate in terms of sex, race, ethnicity, and atopic history. All patients denied a previous history of angioedema and could not identify an alternative trigger immediately before symptom onset. The only commonality among these patients was the administration of an mRNA COVID-19 vaccine hours or days before the onset of symptoms. This suggests, but by no means proves, causality between the vaccine administration and development of delayed urticaria and angioedema. The lifetime prevalence of urticaria is approximately 9%,⁸ and it is estimated that approximately 1% of the general population is likely to experience an episode of angioedema.⁹ We, thus, cannot exclude the possibility that the episodes of angioedema reported here were simply the incident case of chronic spontaneous angioedema in each of these patients; however, so far, none have had a second episode.

In summary, we report 3 distinct cases of angioedema that occurred within days of receiving an mRNA COVID-19 vaccine severe enough to warrant an ED visit. From the clinical history, no factor was identified that could have predicted that angioedema (or the severity) would develop in each case. Fortunately, all patients were successfully treated, and no deaths occurred. Such cases of delayed angioedema seem to be rare and, interestingly, patient 2 received the second vaccine dosage without complications or delayed angioedema. Whereas patients and clinicians need to be aware of the risk of adverse reactions, including the possibility of delayed angioedema after administration of a novel mRNA COVID-19 vaccine, the benefits of receiving the COVID-19 vaccine continue to outweigh the risk of a potential adverse reaction occurring for most individuals.

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